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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/690,063	IKEDA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *5,6 and 10-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/20/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-20 are pending.

Priority

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

The provisional application is missing from the first sentence of the specification.

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/420,348, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application.

Instant claims 4 and 7 do not have written support under 112 first paragraph in provisional application '348. Thus, instant claims 4 and 7 only have priority to the instant application.

Election/Restrictions

This application contains claims directed to the following patentably distinct species of the claimed invention: anti-inflammatory cytokine is one or more cytokines selected from the group consisting of IL-10, Il-1ra, IL-4, IL-13, TNFsr, alpha-MSH, and TGF-Beta1 in instant claim 2.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

This application contains claims directed to the following patentably distinct species of the claimed invention: a recombinant vector selected from a recombinant virus in claims 5 and 6 and claims 10-20 or plasmid DNA in claim 7.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claim 1 is generic.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Roberta Robins on 11/02/05 a provisional election was made without traverse to prosecute the elected species Il-10 in claims 2-4 and elected species plasmid DNA in claim 7. Affirmation of this election must be made by applicant in replying to this Office action. Claims 5, 6, and 10-20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 7-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a vascular disease in a vertebrate subject comprising administering to said subject a recombinant vector comprising a nucleic acid encoding an anti-inflammatory cytokine (IL-10), wherein the nucleic acid is operably linked to a promoter, does not reasonably provide enablement for preventing a vascular disease in a vertebrate subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to a method of treating or preventing a vascular disease in a vertebrate subject comprising using a genus of administrations routes to administer a recombinant vector comprising control elements operably linked to a nucleic acid encoding an anti-inflammatory cytokine (IL-10). The method is further directed to using the method in humans. Thus, the claims are considered broad.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (United States v. Technologies Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather a

conclusion reached by many factors. These factors were outlined in Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in In Re Wands (see above).

Furthermore, and with respect to claims directed to any gene therapy treatment of a vertebrate subject; the state of the art exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any gene therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). For additional reviews of the unpredictability of gene therapy art, see Kmiec, American Scientist, 1999, 87, 240-247; Juengst, BMJ, 2003, 326:1410-11; Khurana et al. Hypertension 2001, 38:1210-1216; Isner et al. Circulation Research 2001, 89:389-400.

Therefore, at the time the application was filed, the state of the art for gene therapy was considered unpredictable.

With respect to the working examples, the applicants teach the effect of rAAV-Il-10 on C2C12 mouse myoblasts in vitro. In addition, the applicants teach using rAAV-Il-10 to modulate the atherosclerotic process in ApoE-deficient mice and the reduction of hypertension in stroke-prone spontaneously hypertensive rats.

The claimed invention embraces treating or preventing a genus of vascular disease in a vertebrate subject using a recombinant vector comprising a nucleic acid encoding anti-inflammatory cytokine (e.g., IL-10). Thus, the claimed are considered broad. In view of the prior art (French et al., US 6290949) and the teaching in the specification, the specification provides sufficient guidance and/or factual evidence for treating a vascular disease in a

vertebrate subject using a recombinant vector comprising an anti-inflammatory cytokine (IL-10). However, with respect to preventing a vascular disease in a vertebrate subject using the claimed method, the applicant provides no working example of preventing a vascular disease in a vertebrate subject. The invention involves one of the most complex areas of medicine/molecular biology, gene therapy for the treatment of vascular disease in vertebrate subjects (humans). The gene therapy art at the time the invention of applicants invention was nil with no demonstrated evidence of an unambiguous successful gene therapy procedure for preventing a vascular disease in a human. The prior art teaches that, "IL-10 does not cross the intact blood/brain barrier in appreciable amounts, has a short half life such that sustainable delivery for prolonged periods would be difficult, has not been successfully delivered orally, so presents problems for systemic administration, and would disrupt the normal functions of the body's immune system and would be expected to be detrimental to the health of the patient." See Watkins, US 20040258671. There are major concerns for any method of gene therapy including *in vivo* gene therapy for preventing a vascular disease in a subject that the specification fails to address and some of the major concerns are:

1) what amount of the expressed anti-inflammatory cytokine is considered to be therapeutically effective for preventing vascular disease in a subject;
2) what defines "preventing" a vascular disease in a subject;
3) what would one skilled in the art compare the claimed method to in order to ascertain that preventing vascular disease was obtained.

Furthermore, with respect to claim 4 directed to treating or preventing a vascular disease in a human, applicants teach treating ApoE-deficient mice and stroke-prone spontaneously hypertensive rats using the claimed method. However, the relevance of this data to treatment or preventing a vascular disease in a human is unclear at because neither the applicants nor the prior

art provide a correlation or nexus between the results obtained in in vitro and in vivo studies such as those provided by applicants with results which the skilled artisan would reasonably expect to see when practicing the claimed invention with humans.

In conclusion, the specification and claims coupled with the art of record, at the time the invention was made, do not provide sufficient guidance and/or factual evidence for practicing the full scope of the claimed invention. Given that gene therapy wherein any recombinant vector is employed to treat or prevent a disease or a medical condition in any vertebrate subject was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any recombinant vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 7, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by French et al. (US 6290949). French teaches gene therapy for coronary artery restenosis, wherein the therapeutic DNA can encode IL-10 and the DNA is operably linked to control elements (columns 10-12, 16-18, and 34-36). French teaches that the DNA sequence can be in a either viral vector or a plasmid (column 13).

Claims 1-3 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Moldawer et al. (US 6086868). Moldawer teaches using gene therapy for treating ischemia reperfusion injury using a mammalian expression plasmid comprising IL10 (column 2). Moldawer teaches that the administration can be by intramuscular injection or intravenous administration (column 5).

Claims 1, 2, 3, and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by von der Thusen et al. (FASEB J., 15:2730-2732, 2001). von der Thusen teaches treating vascular disease in a mouse comprising intravenous administration of an adenovirus comprising a nucleic acid encoding Il-10 (page 2730). von der Thusen does not specifically teach that the nucleic acid is operably linked to control elements, but the IL-10 is expressed in vivo indicating that the nucleic acid was operably linked to control elements.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over von der Thusen et al. (FASEB J., 15:2730-2732, 2001) taken with Moldawer et al. (US 6086868). von der Thusen teaches treating vascular disease in a mouse comprising intravenous administration of an adenovirus comprising a nucleic acid encoding Il-10 (page 2730). von der Thusen does not specifically teach that the nucleic acid is operably linked to control elements, but the IL-10 is expressed in vivo indicating that the nucleic acid was operably linked to control elements. However, von der Thusen does not specifically teach using a plasmid instead of an adenovirus in the method.

However, at the time the invention was made, Moldawer teaches that delivering and expressing a nucleic acid encoding IL10 to a mammal using either a plasmid or viral vectors was well known to one of ordinary skill in the art (column 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of von der Thusen taken with Moldawer, namely to use a plasmid to deliver the nucleic acid in the method of treating a vascular disease in a mouse. One of ordinary skill in the art would have been motivated to combine the teaching, as matter of designer's choice, and use a plasmid instead of an adenovirus in the method because both vectors would result in sufficiently expressing the protein in the mouse to treat a vascular disease in the mouse. See Moldawer, column 2.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Yamaoka et al., Japanese Circulation Journal, 63: 951-956, 1999, teaches that IL-10 may be an important inherent component of the cytokine network of congestive heart failure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Brian Whiteman
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